Treatment of chronic hepatitis C genotype 1 with triple therapy comprising telaprevir or boceprevir

Moradpour, Darius ; Müllhaupt, Beat ; Swiss Association for the Study of the Liver

Abstract: Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma worldwide. Two first-generation protease inhibitors, telaprevir and boceprevir, have recently been approved for the treatment of chronic hepatitis C genotype 1. Triple therapy comprising pegylated interferon- , ribavirin and telaprevir or boceprevir increases sustained virological response rates to 70% and allows to shorten treatment duration in ½ of treatment-naïve patients with chronic hepatitis C genotype 1. Sustained virological response rates in treatment-experienced patients depend on the response to previous treatment, ranging from >80% in previous relapsers to 30% in previous null responders. These advances come at the expense of new adverse effects and increased cost. In addition, treatment of chronic hepatitis C will become more complex. In these times of changing medical practice, the present expert opinion statement by the Swiss Association for the Study of the Liver shall provide guidance on the treatment of chronic hepatitis C with triple therapy comprising telaprevir or boceprevir.

DOI: https://doi.org/10.4414/smw.2012.13516

Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article | Published 24 February 2012, doi:10.4414/smw.2012.13516
Cite this as: Swiss Med Wkly. 2012;142:w13516

Treatment of chronic hepatitis C genotype 1 with triple therapy comprising telaprevir or boceprevir

Swiss Association for the Study of the Liver[1]

[1] Current Council Members of the Swiss Association for the Study of the Liver are listed in www.sasl.ch.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BOC, boceprevir; CHC, chronic hepatitis C; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PEG-IFN-α, pegylated interferon-α; RBV, ribavirin; SVR, sustained virological response; SASL, Swiss Association for the Study of the Liver; TPV, telaprevir.

Summary

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma worldwide. Two first-generation protease inhibitors, telaprevir and boceprevir, have recently been approved for the treatment of chronic hepatitis C genotype 1. Triple therapy comprising pegylated interferon-α, ribavirin and telaprevir or boceprevir increases sustained virological response rates to ~70% and allows to shorten treatment duration in ~½ of treatment-naïve patients with chronic hepatitis C genotype 1. Sustained virological response rates in treatment-experienced patients depend on the response to previous treatment, ranging from >80% in previous relapsers to ~30% in previous null responders. These advances come at the expense of new adverse effects and increased cost. In addition, treatment of chronic hepatitis C will become more complex. In these times of changing medical practice, the present expert opinion statement by the Swiss Association for the Study of the Liver shall provide guidance on the treatment of chronic hepatitis C with triple therapy comprising telaprevir or boceprevir.

Key words: *boceprevir; chronic hepatitis C; HCV; hepatitis C virus; interferon; protease inhibitor; ribavirin; telaprevir*

Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) [1–3]. An estimated 120–200 million individuals worldwide and about 1% of the general population in Switzerland are chronically infected with HCV. About 50% of the chronic HCV infections in Switzerland are due to genotype 1 [4]. While the incidence of acute hepatitis C has declined significantly since the introduction of anti-HCV screening of blood and blood products in 1990, the number of patients presenting with decompensated cirrhosis and HCC is expected to increase further, attaining a peak around 2020 [1, 5]. More than 50% of the individuals at risk may currently be unaware of their infection. Strategies to increase testing and detection rates are currently being explored (e.g., screening of populations at risk *vs.* birth cohort screening) [6, 7].

Fifty to 80% of acutely infected individuals develop persistent infection. Of these, 2–20% will develop liver cirrhosis within the first 20 years, and accumulating evidence suggests that disease progression may increase in a nonlinear fashion thereafter [8]. Once cirrhosis is established, the rate of HCC development is 1–6% per year. Factors associated with more frequent and rapid progression to cirrhosis are, among others, higher age at the time of infection, male sex, alcohol consumption, coinfections with the human immunodeficiency virus (HIV) or hepatitis B virus (HBV), nonalcoholic fatty liver disease and smoking. Comprehensive management of chronic hepatitis C (CHC) takes these factors into consideration and aims at improving the ones that can be modified (alcohol abstinence; weight loss, regular physical activity and other measures to control the metabolic syndrome; vaccination against HBV [and hepatitis A virus]; smoking cessation including cannabis) [9].

While non-invasive methods for fibrosis assessment are actively being pursued [10], liver biopsy remains the reference for grading and staging of CHC. The Metavir and Ishak scoring systems are most often applied. Fibrosis stages are classified from 0 (absence of fibrosis) to 4 (cirrhosis) in the Metavir system [11], and from 0 to 6 in the Ishak system [12].

The decision to treat CHC is based on the analysis of numerous variables and should take into account the specific situation of each patient. Treatment is clearly recommended for patients with Metavir fibrosis stage ≥2 who do not have any contraindications. For other patients, decisions will have to be made on an individual basis. Additional

factors that come into consideration are, among others, the (biological) age and general condition of the patient, the patient's personal and professional plans, the duration of HCV infection, the risk of developing cirrhosis, the likelihood of response to therapy, and comorbidity.

For the last 10 years, standard therapy of CHC consisted of pegylated interferon-α (PEG-IFN-α) combined with ribavirin (RBV) for (16-)24-48(-72) weeks, yielding sustained virological response (SVR) rates of 40–50% in patients infected with HCV genotype 1 and ~80% in patients infected with genotypes 2 and 3. Definitions of virological response patterns are provided in table 1.

Polymorphisms near the *IL28B* gene have recently been identified as strong predictors of the outcome of IFN-α-based antiviral therapy (reviewed in [13, 14]). A number of laboratories offer *IL28B* genetic testing, but its role in clinical practice and decision making, if any, remains to be defined.

A first generation of directly acting antivirals, the NS3-4A protease inhibitors telaprevir (TPV; Incivo®) and boceprevir (BOC; Victrelis®), has recently been approved for the treatment of CHC genotype 1. TPV and BOC have to be combined with PEG-IFN-α and RBV in order to avoid the rapid selection of HCV strains resistant to antiviral therapy [15, 16]. Triple therapy comprising TPV or BOC increases SVR rates to ~70% in treatment-naïve patients with CHC genotype 1 [17–19]. In treatment-experienced patients, SVR rates depend on the virological response to previous therapy with PEG-IFN-α and RBV, ranging from >80% in patients with previous relapse to ~50% in patients with previous partial response and ~30% in patients with previous null response [20–22]. Treatment schedules comprising TPV or BOC have more side effects than PEG-IFN-α and RBV, and should be managed carefully.

A significant increase in the number of patients with CHC to be treated is expected for 2012, with triple therapy regimens that are more complex, as discussed below [23]. These expected developments represent a significant challenge and will stretch current resources.

The present Swiss Association for the Study of the Liver (SASL) expert opinion statement is not intended as guideline but shall provide some guidance on the management of CHC genotype 1 and the use of TPV and BOC. It is based on the results of recently published phase III clinical trials performed in treatment-naïve and treatment-experienced patients (ADVANCE [17], ILLUMINATE [19] and REALIZE [20] for TPV as well as SPRINT-2 [18], RESPOND-2 [21] and PROVIDE [22] for BOC), and take into account the recently updated American Association for the Study of Liver Diseases (AASLD) Practice Guidelines [3] as well as the labels approved by the US Food and Drug Administration, the European Medicinal Agency, and Swissmedic. Current European Association for the Study of the Liver (EASL) Clinical Practice Guidelines [2] are expected to be updated shortly. In addition, different national guidelines are in preparation. Therefore, as recommendations are emerging and as real-life data and practical experience on the use of TPV and BOC are still limited, it is strongly recommended to initiate and pursue triple therapy comprising TPV or BOC only in close collaboration with an expert centre.

Practical use of telaprevir and boceprevir

TPV is available in the form of 375-mg film-coated tablets and has to be taken at a dose of 750 mg every 8 hours (i.e., two tablets every 8 hours), with a meal or a snack containing ~20 g of fat to increase bioavailability. BOC is available in the form of 200-mg capsules and has to be taken at a dose of 800 mg every 8 hours (i.e., 4 capsules every 8 hours), with a meal or a snack. Dosing every 8 ± 1 hour rather than 3 times per day is important to maintain inhibitory drug serum concentrations and to avoid antiviral resistance development. TPV and BOC should never be used alone, and doses should never be reduced. When used alone, these drugs will not be effective and will cause emergence of HCV strains with resistance to antiviral therapy that could be difficult to treat subsequently. RBV can be taken with the first dose of TPV or BOC in the morning and with the last dose of TPV or BOC in the evening.

TPV and BOC are only approved for use in patients with HCV genotype 1 infection. The development of antiviral resistance is more frequent in subtype 1a than 1b but this should not influence therapeutic decision making.

Table 1: Definition of virological response patterns.

Rapid virological response (RVR)	Undetectable[1] HCV RNA at week 4
Extended RVR (eRVR)	Undetectable HCV RNA at weeks 4 and 12[2]
RVR8	Undetectable HCV RNA at week 8[3]
Early virological response (EVR)	>2 log drop of HCV RNA at week 12
Complete EVR (cEVR)[4]	Undetectable HCV RNA at week 12
Partial EVR (pEVR)	>2 log drop but still detectable HCV RNA at week 12
Delayed virological response (DVR)[5]	>2 log drop but still detectable HCV RNA at week 12, undetectable HCV RNA at week 24
Partial response (PR)	>2 log drop of HCV RNA at week 12 but detectable at weeks 12 and 24
Null response (NR)	<2 log drop of HCV RNA at week 12
Breakthrough (BT)	Reappearance of HCV RNA at any time during treatment
Relapse	HCV RNA undetectable at end of treatment but detectable within 24 wks of follow-up
Sustained virological response (SVR)	Undetectable HCV RNA 24 weeks after the end of treatment

[1] The term "undetectable" in this paper refers to HCV RNA below the limited of detection (as opposed to the limit of quantitation) of a sensitive real-time PCR assay.
[2] Relates to triple therapy comprising telaprevir.
[3] Relates to triple therapy comprising boceprevir, including a 4-week lead-in phase of pegylated interferon-α and ribavirin.
[4] Designated as early virological response in the recent EASL Clinical Practice Guidelines (ref. 2).
[5] Formerly designated as slow virological response.

Both TPV and BOC have a strong potential for drug-drug interactions, as they affect the metabolism of other drugs metabolised through cytochrome P450 3A4 (CYP3A4) and other pathways [24]. See package inserts, continuously updated online databases (e.g., http://www.hep-druginteractions.org, Epocrates, Medscape) and Leise et al. [25] for known drug-drug interactions and contraindicated drugs. Commonly used drugs that are contraindicated in combination with TPV or BOC include, among others, atorvastatin, lovastatin, simvastatin, sildenafil, alfuzosin, carbamazepin, phenytoin, oral midazolam, and St. John's wort. Among the drugs commonly used to manage adverse effects of therapy, paracetamol and metoclopramide (but not domperidone) are allowed. TPV and BOC may decrease citalopram levels and efficacy.

Main adverse effects of TPV include anemia, nausea and diarrhea, skin rashes and pruritus as well as anorectal disorders. Rash should be managed in collaboration with an experienced dermatologist and should follow recommendations that have recently been summarised [26]. TPV has to be discontinued if rash progresses and becomes severe. Rare cases of DRESS (drug-related eosinophilia with systemic symptoms) and Stevens Johnson syndrome/toxic epidermal necrolysis have been observed. If either one is suspected, all drugs have to be stopped immediately, followed by emergency dermatological consultation.

Main adverse effects of BOC include anemia, with a significant number of patients requiring concomitant erythropoietin treatment in phase II and III clinical trials, as well as dysgeusia.

Anemia can develop rapidly and become very pronounced with both TPV and BOC, especially in patients with cirrhosis. Therefore, close monitoring is recommended. Anemia should be managed by timely RBV dose reduction and, if needed, blood transfusions and/or erythropoetin.

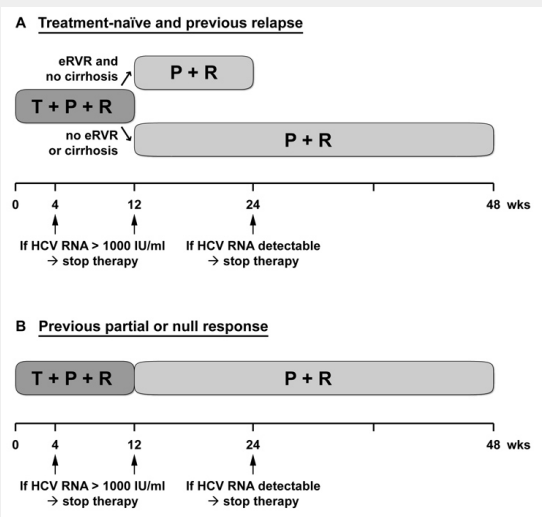

Figure 1

Telaprevir-based triple therapy. (A) Treatment-naïve patients with CHC genotype 1 and treatment-experienced patients with previous relapse. (B) Treatment-experienced patients with CHC genotype 1 and previous partial or null response. eRVR, extended rapid virological response (see table 1 for definitions of virological response patterns); P, pegylated interferon-α; R, ribavirin; T, telaprevir; wks, weeks.

Data on the safety and efficacy of TPV and BOC in patients with HIV coinfection are emerging. TPV and BOC should be used only in close collaboration with an expert in these patients.

There is no data in liver transplant recipients, hemodialysis patients and children, and the use of TPV and BOC in these situations is currently proscribed.

In registration trials, TPV was used with PEG-IFN-α2a 180 µg per week plus RBV 1000–1200 mg per day and BOC was used with PEG-IFN-α2b 1.5 µg/kg per week plus RBV 600–1400 mg per day. However, both forms of PEG-IFN-α may be used with RBV and either TPV or BOC.

PEG-IFN-α is contraindicated in decompensated cirrhosis.

Strict contraception must be followed during and for 6 months after the end of triple therapy because of the potential teratogenicity of RBV.

Who should be treated with triple therapy comprising TPV or BOC?

Triple therapy will represent a new standard for most treatment-naïve patients with CHC genotype 1 as well as treatment-experienced patients with a relapse or partial response to previous therapy with PEG-IFN-α and RBV (table 2).

Treatment of CHC is expected to change significantly within the next few years, with the arrival of better tolerated and

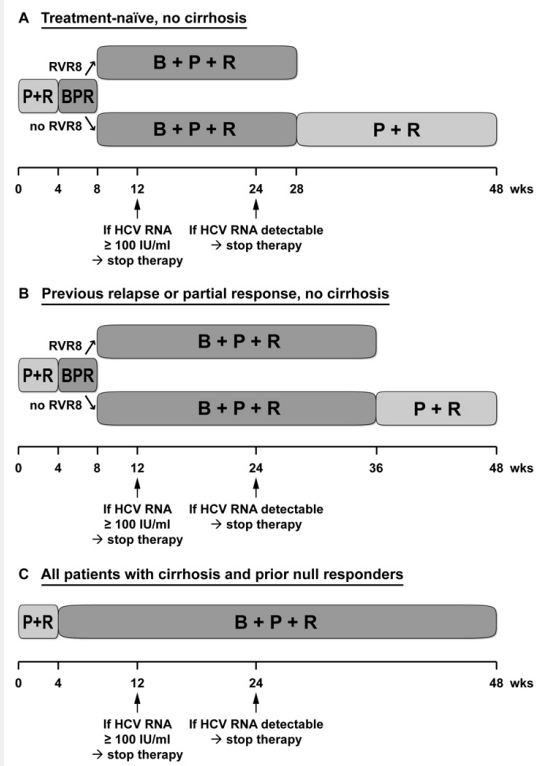

Figure 2

Boceprevir-based triple therapy. (A) Treatment-naïve patients with CHC of genotype 1 without cirrhosis. (B) Treatment-experienced patients with CHC genotype 1 and previous relapse or partial response without cirrhosis. (C) All cirrhotic patients and prior null responders. B, boceprevir; BPR = B + P + R; P, pegylated interferon-α; R, ribavirin; RVR8, rapid virological response at week 8 (see table 1 for definitions of virological response patterns); wks, weeks.

even more efficacious new drugs as well as the advent of IFN-free/sparing regimens [27–30]. These developments shall significantly improve the outlook for our patients. Therefore, deferring treatment may be considered in patients who's treatment can be safely postponed.

Treatment-naïve patients with favourable baseline predictors (HCV RNA <4 x 10^5 IU/ml, absence of advanced fibrosis or cirrhosis) who achieve a rapid virological response (RVR; see table 1) have excellent chances to achieve SVR with 24 weeks of therapy with PEG-IFN-α and RBV alone [31]. Therefore, a 4-week lead-in with PEG-IFN-α and RBV may be considered in patients with the above-mentioned favourable baseline predictors and treatment continued without adding TPV or BOC for a total of 24 weeks in those who achieve RVR.

Lead-in with PEG-IFN-α and RBV may also be considered if there are doubts concerning the tolerance or adherence to PEG-IFN-α and RBV backbone therapy.

There is currently only limited data on the use of BOC in patients with previous null response. In general, retreatment of previous null responders has to be considered carefully, as SVR rates remain limited, especially in patients with cirrhosis. Inclusion of such patients into clinical trials involving quadruple therapy or IFN-sparing regimens may be considered. Lead-in with PEG-IFN-α and RBV may be considered in previous null responders, especially in cirrhotics, with the addition of TPV or BOC only in case of ≥1 log decline of HCV RNA at week 4. Subanalysis of the REALIZE trial revealed that 54% of the patients with ≥1 log decline after 4 weeks of lead-in with PEG-IFN-α and RBV achieved SVR with triple therapy comprising TPV, compared to only 15% of those with a decline of HCV RNA <1 log [32].

Careful monitoring and stopping rules, as detailed below, shall reduce the risk of selecting HCV strains resistant to antiviral therapy. While long-term consequences of the selection of such strains are presently unknown, antiviral resistance is likely to affect future treatment options [15, 16].

Specific treatment algorithms

Telaprevir-based triple therapy

• Treatment-naïve patients and previous relapsers with CHC genotype 1 (fig. 1A)

Non-cirrhotic patients who achieve eRVR
12 weeks TPV + PEG-IFN-α + RBV
+ 12 weeks PEG-IFN-α + RBV

Non-cirrhotic patients who do not achieve eRVR and all cirrhotic patients
12 weeks TPV + PEG-IFN-α + RBV
+ 36 weeks PEG-IFN-α + RBV

• Previous partial and null responders with CHC genotype 1 (fig. 1B)

12 weeks TPV + PEG-IFN-α + RBV
+ 36 weeks PEG-IFN-α + RBV

Lead-in with PEG-IFN-α and RBV may be considered in previous null responders, especially in cirrhotics, with the addition of TPV only in case of ≥1 log decline of HCV RNA at week 4.

Stopping rules:
– Stop all therapy if HCV RNA >1000 IU/ml at either week 4 or 12 of triple therapy.
– Stop all therapy if HCV RNA detectable at wk 24.
– Stop all therapy if previously negative HCV RNA becomes confirmed positive again under treatment.

Table 2: Who should be treated with triple therapy comprising telaprevir (TPV) or boceprevir (BOC)?

- Treatment-naïve patients with CHC genotype 1
  - → Triple therapy new standard for most patients.
  - → Consider PEG-IFN-α and RBV lead-in
    - in patients with favorable baseline predictors (HCV RNA <4 x 10^5 IU/ml, lack of advanced fibrosis or cirrhosis);
    - in case of doubt concerning adherence to PEG-IFN-α and RBV backbone.
- CHC genotype 1 relapsers or partial responders to previous treatment with PEG-IFN-α and RBV
  - → Retreat with triple therapy.
  - → Consider PEG-IFN-α and RBV lead-in in case of doubt concerning adherence to PEG-IFN-α and RBV backbone.
- CHC genotype 1 null responders to previous treatment with PEG-IFN-α and RBV
  - → Carefully consider retreatment with triple therapy *vs.* await quadruple therapy or IFN-sparing regimens.
  - → Consider PEG-IFN-α and RBV lead-in.
- Patients with genotypes other than 1
  - → PEG-IFN-α and RBV.

CHC, chronic hepatitis C; PEG-IFN-α, pegylated interferon-α; RBV, ribavirin.

Table 3: Key points.

- Consider the natural history of hepatitis C and factors affecting disease progression.
- Considerate treatment indication crucial (Treat the disease, not the infection!).
- Triple therapy comprising TPV or BOC increases SVR rates to ~70%, with shortened treatment duration in ~½.
- Advances will come at the expense of new adverse effects and increased cost.
- Antiviral therapy will become more complex (patient education, adherence, treatment milestones, adverse effect management, laboratory infrastructure and turnaround time, antiviral resistance).
- Limited or no data in patients with high unmet need (especially those with HIV coinfection and recurrent hepatitis C after liver transplantation).
- Available resources will be stretched.
- Liaise with an expert center.

Boceprevir-based triple therapy

• **Treatment-naïve patients with CHC genotype 1** (fig. 2A and 2C)

Non-cirrhotic patients who achieve RVR8
4 weeks PEG-IFN-α + RBV lead-in
+ 24 weeks BOC + PEG-IFN-α + RBV

Non-cirrhotic patients who do not achieve RVR8
4 weeks PEG-IFN-α + RBV lead-in
+ 24 weeks BOC + PEG-IFN-α + RBV
+ 20 weeks PEG-IFN-α + RBV

Cirrhotic patients
4 weeks PEG-IFN-α + RBV lead-in
+ 44 weeks BOC + PEG-IFN-α + RBV

• **Previous relapsers or partial responders with CHC genotype 1*** (fig. 2B and 2C)

Non-cirrhotic patients who achieve RVR8
4 weeks PEG-IFN-α + RBV lead-in
+ 32 weeks BOC + PEG-IFN-α + RBV

Non-cirrhotic patients who do not achieve RVR8
4 weeks PEG-IFN-α + RBV lead-in
+ 32 weeks BOC + PEG-IFN-α + RBV
+ 12 weeks PEG-IFN-α + RBV*

Cirrhotic patients
4 weeks PEG-IFN-α + RBV lead-in
+ 44 weeks BOC + PEG-IFN-α + RBV

*For patients with prior null response, 4 weeks of lead-in with PEG-IFN-α + RBV, followed by 44 weeks of triple therapy with BOC + PEG-IFN-α + RBV is recommended.

Stopping rules:
– Consider stopping therapy in patients with cirrhosis and <1 log drop of HCV RNA after lead-in (chances of achieving SVR being 13–25% only [33]).
– Stop all therapy if HCV RNA ≥100 IU/ml at week 12.
– Stop all therapy if HCV RNA detectable at week 24.
– Stop all therapy if previously negative HCV RNA becomes confirmed positive again under treatment.

Conclusions

Key points are summarised in table 3.

Funding / potential competing interests: SASL or the SASL Council Members have not received any financial support in relation with the writing of this article. DM and BM as corresponding authors assume responsibility for the integrity of this article. Both have received research support from MSD and Roche and have acted as advisors to Janssen, MSD and Roche.

Correspondence: *Professor Darius Moradpour, MD, Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Rue du Bugnon 44, CH-1011 Lausanne, Switzerland,*
darius.moradpour[at]chuv.ch
or
Professor Beat Müllhaupt, MD, Division of Gastroenterology and Hepatology, University Hospital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland, beat.muellhaupt[at]usz.ch

References

1 Nature Outlook: Hepatitis C. Nature. 2011;474:S1–S21.
2 EASL Clinical Practice Guideline: Management of hepatitis C virus infection. J Hepatol. 2011;55:245–64.
3 Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 Practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54:1433–44.
4 Prasad L, Spicher VM, Zwahlen M, et al. Cohort Profile: the Swiss Hepatitis C Cohort Study. Int J Epidemiol. 2007;36:731–7.
5 Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138:513–21.
6 McGarry LJ, Pawar VS, Parekh HH, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatology. 2012, in press.
7 Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012, in press.
8 Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48:418–31.
9 Missiha SB, Ostrowski M, Heathcote EJ. Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. Gastroenterology. 2008;134:1699–714.
10 Pinzani M, Vizzutti F, Arena U, et al. Noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nat Clin Pract Gastroenterol Hepatol. 2008;5:95–106.
11 Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24:289–93.
12 Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22:696–9.
13 Rauch A, Rohrbach J, Bochud PY. The recent breakthroughs in the understanding of host genomics in hepatitis C. Eur J Clin Invest. 2010;40:950–9.
14 Lange CM, Zeuzem S. *IL28B* single nucleotide polymorphisms in the treatment of hepatitis C. J Hepatol. 2011;55:692–701.
15 Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. Gastroenterology. 2010;138:447–62.
16 Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. J Hepatol. 2011;55:192–206.
17 Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364:2405–16.
18 Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1195–206.
19 Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365:1014–24.
20 Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364:2417–28.

21 Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011;364:1207–17.

22 Vierling JM, Flamm SL, Gordon SC, et al. Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: the PROVIDE Study. Hepatology. 2011;54(Suppl 1):796A.

23 Deuffic-Burban S, Mathurin P, Pol S, et al. Impact of hepatitis C triple therapy availability upon the number of patients to be treated and associated costs in France: a model-based analysis. Gut. 2012;61:290–6.

24 Garg V, van Heeswijk R, Eun Lee J, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011;54:20–7.

25 Leise MD, Kim WR, Canterbury KM, et al. Drug therapy: Telaprevir. Hepatology 2011;54:1463-1469.

26 Cacoub P, Bourlière M, Lübbe J, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. J. Hepatol. 2012;56:455–63.

27 Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2010;376:1476–5.

28 Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders. Hepatology. 2012, in press.

29 Gane EJ, Stedman CA, Hyland RH, et al. Once daily PSI-7977 plus RBV: pegylated interferon-alfa not required for complete rapid viral response in treatment-naïve patients with HCV gt 2 or gt 3. Hepatology. 2011;54(Suppl 1):377A.

30 Lok ASF, Gardiner D, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366:216–24.

31 Di Martino V, Richou C, Cervoni JP, et al. Response-guided peg-interferon plus ribavirin treatment duration in chronic hepatitis C: Meta-analyses of randomized, controlled trials and implications for the future. Hepatology. 2011;54:789–800.

32 Foster GR, Zeuzem S, Andreone P, et al. Subanalyses of the telaprevir lead-in arm in the REALIZE study: response at week 4 is not a substitute for prior null response categorization. J Hepatol. 2011;54(Suppl 1):S3.

33 Bruno S, Vierling JM, Esteban R, et al. Boceprevir in addition to standard of care enhanced SVR in hepatitis C virus genotype 1 with advanced fibrosis/cirrhosis: subgroup analysis of SPRINT-2 and RESPOND-2 studies. J Hepatol. 2011;54(Suppl 1):S4.

Figures (large format)

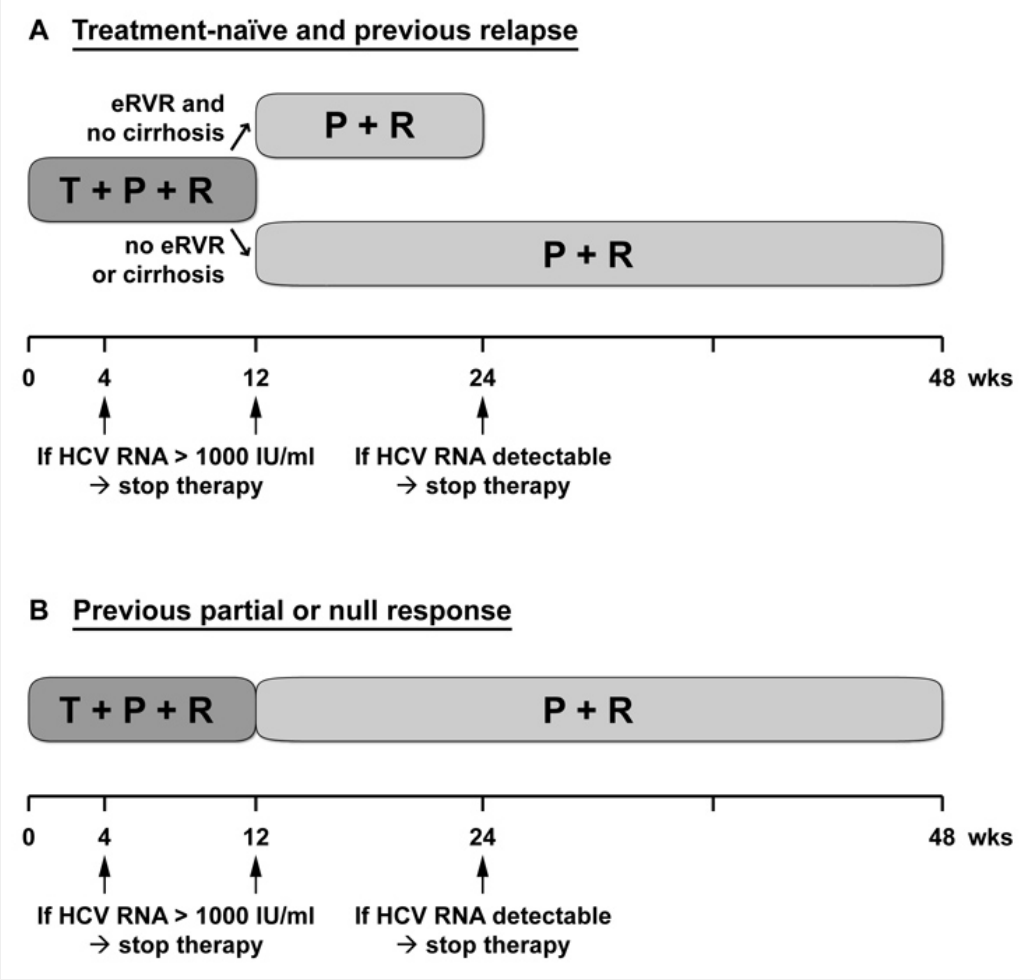

Figure 1

Telaprevir-based triple therapy. (A) Treatment-naïve patients with CHC genotype 1 and treatment-experienced patients with previous relapse. (B) Treatment-experienced patients with CHC genotype 1 and previous partial or null response. eRVR, extended rapid virological response (see table 1 for definitions of virological response patterns); P, pegylated interferon-α; R, ribavirin; T, telaprevir; wks, weeks.

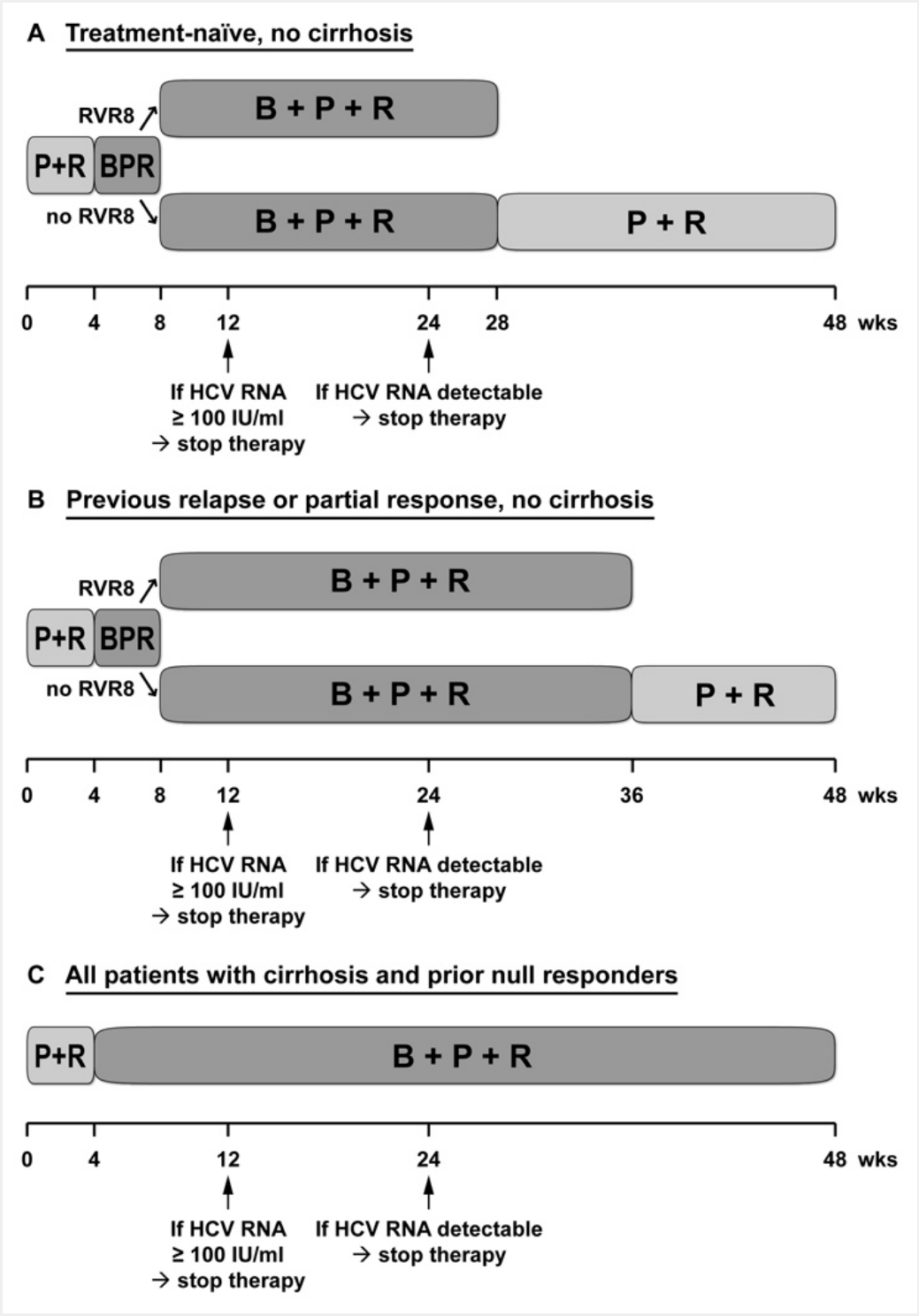

Figure 2

Boceprevir-based triple therapy. (A) Treatment-naïve patients with CHC of genotype 1 without cirrhosis. (B) Treatment-experienced patients with CHC genotype 1 and previous relapse or partial response without cirrhosis. (C) All cirrhotic patients and prior null responders. B, boceprevir; BPR = B + P + R; P, pegylated interferon-α; R, ribavirin; RVR8, rapid virological response at week 8 (see table 1 for definitions of virological response patterns); wks, weeks.